Review article

3P's (Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic) of Valproate: What's New?

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Abstract

Valproate (VPA) has been used clinically for more than 40 years and remains one of the most commonly prescribed antiepileptic drugs. With the advances of various scientific disciplines, much new information about this drug has been uncovered. The aim of this review is to summarize new knowledge about the pharmacokinetics, pharmacodynamics, and pharmacogenomics (3Ps) of VPA for future applications and studies. The review was identified nonsystematically using Pubmed, Google Scholar, and open-access search engines, and studies on the pharmacokinetics, pharmacodynamics, and pharmacogenomics of VPA between 2012 and 2022 were included. Recent findings on pharmacokinetic information, including factors associated with serum VPA levels and its interaction with new drugs. On the other hand, VPA was found to have a neuroprotective effect that is beneficial in brain disorders as well as in patients with c stroke. With respect to the lungs, it has been found to reduce the risk of acute respiratory failure. Recent risk data linked VPA use to hepatotoxicity, vitamin D deficiency, prolonged QT interval, and insulin resistance, among others. Various gene polymorphisms such as CYP2C9 and UGT1A6 are some polymorphisms that may cause dose alteration in the population. The compilation of the 3Ps of VPA revealed new drug information indicating the need for further evaluation. These include new uses and benefits, toxicity data including acute and chronic use, and the involvement of genetic polymorphisms in the pharmacokinetics and pharmacodynamics of the drug.

Keywords: Sodium valproate, pharmacokinetic, pharmacodynamic, pharmacogenomic.

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1.0 Introduction

Sodium valproate (sodium 2-propylpentanoic acid, VPA) was first approved for the treatment of epilepsy in France in 1967 (1), although a controlled trial was not published until 1975 (2). This drug was used as a first-line therapy for generalised tonic-clonic seizures and later found to be useful for non-epileptic seizures as well as manic episodes of bipolar disorder and prophylaxis of migraine (3). Its use found to be associated with an increased risk of fatigue, digestive problems, weight gain, tremors, baldness, thrombocytopenia and changes in liver enzymes. (4).

Though VPA is a well studied compound, recent studies unearthed much more information about VPA. At the cellular level, VPA was found to act on histone deacetylases (HDACs), ion channels, phospholipase A2 signalling and inositol synthesis, among others (5). These complex mechanisms may be responsible for some of the effects of VPA that may have been previously overlooked.

Aside new uses of VPA were reported among others include as the treatment of alcohol dependency (6), as an abortive agent in prolonged migraine attacks (7) and many others.

In recent years, the interest in the influence of genetic factors and valproate such as the effect of T1405 polymorphism in the carbamoyl phosphate synthetase 1 (CPS1) gene on valproate-induced hyperammonemia (8), the association of chronic liver condition and elevated serum concentration of γ-glutamyltransferase (γ-GT) (9) and many others.

With new knowledge of VPA being uncovered, it is important to compile these findings for future applications and studies. The studies were unsystematically indentified using various libraries including Pubmed, Google Scholar and any open access search engines. VPA studies in the between 2012 to 2022 were included in the review.

2.0 Pharmacokinetics of VPA

2.1 Absorption

VPA is well absorbed with a bioavailability of more than 80%. The peak plasma level of VPA was reached at 3 to 4 hours after oral administration and the steady state at 24 to 48 hours (1). The plasma half-life of VPA is 10 to 16 hours and is administered 3 to 4 times per day (10). The unbound component is pharmacologically active and able to cross the blood-brain barrier (1). The presence of food delays the absorption of VPA. Some drugs, namely carbapenem antibiotics and dolutegravir, decrease serum VPA concentrations by decreasing intestinal absorption (11, 12, 13).

The time to reach the maximum plasma concentration of VPA varies depending on the pharmaceutical preparation (enteric-coated, controlled-release, capsule, liquid, intravenous and suppository). It is estimated that sustained-release formulations require 5 to 10 hours to reach peak concentration after ingestion, whereas syrups require only 2 to 3 hours after ingestion (14).

2.2 Distribution

VPA is highly protein-bound (87-95%) and is mainly bound to albumin, resulting in low clearance (6-20 ml/h/kg) and reduced serum concentration due to saturation of the protein binding site (10). At serum levels below 45-50 μg/ml, the binding sites are unsaturated. At higher serum levels, these binding sites become saturated, increasing the proportion of unbound VPA or leading to higher availability of the unbound drug (1) ranging from 10% at plasma concentrations up to 75 μg/ml to 30% at levels above 150 μg/ml. The average free fraction of VPA in adults on monotherapy ranges from 10% at 40 μg /mL to 18.5% at 130 μg /mL (10).

In the presence of lower serum albumin levels or pregnancy-related hypoalbuminemia (especially during the second and third

trimesters), malnutrition, nephrotic or uraemic disease or liver disease, or concomitant administration of antiepileptic drugs with other high protein drugs (10) VPA levels decrease with high fluctuations in apparent distribution volume (Vd) between 0.1 and 0.5 L/kg (15).

2.3 Metabolism

VPA is mainly metabolised in the liver and excreted in the urine, with only a small amount in unchanged form. In an adult, VPA metabolism involves the glucoronidation by uridine 5'-diphospho-glucoronosyltranferases (UGTs), mitochondrial β-oxidation and metabolism mediated by cytochrome P450 (CYP450). However, in children, glucuronidase activity is much lower than in adults, with mitochondrial β -oxidation being the major pathway in VPA metabolism in children (15). A previous study documented glucuronidation of VPA by UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7 and UGT2B15 in laboratory studies using human liver microsomes and purified recombinant proteins (5).

VPA has also been found to strongly inhibit the isoenzymes UGT, CYP2C19 and epoxide hydrolase, leading to a change in serum concentration of concomitantly taken drugs such as amiodarone, fluconazole, phenylbutazone, sulphinpyrazone, sulphaphenazole and certain other sulphonamides (10).

2.4 Excretion

Approximately 20% of VPA is excreted as a direct conjugate by renal clearance (16). A study in 54 patients reported that high individual variation such as age, body weight, total daily dose and concomitant treatment with other antiepileptic drugs (carbamazepine and phenytoin) were associated with renal clearance of VPA (17).

3.0 Pharmacodynamics of VPA

3.1 Indications

VPA is a United State Food and Drug Administration (USFDA) approved drug for the treatment of various seizure forms including complex partial seizures, against simple and complex absence seizures as monotherapy or adjunctive therapy and in patients with multiple seizure types including absence seizures. It is also approved for the treatment of manic and mixed episodes of bipolar disorder (manic-depressive disorder) and for the prevention of migraine headaches (18).

The off-label uses of VPA among others includes migraine prevention (19) and in management of agitation in dementia (20). Aside, VPA is also was used in the management of neuropathic pain and neuralgia, believed to be via enhanced gamma-aminobutyric acid (GABA) inhibition as described by Wiffen et al through their Cochrane review (21). Another commonly known off-label uses of VPA in psychiatric setting other than bipolar include in the treatment of mania in schizoaffective disorder (22) as well as bahavioral disturbances in children such as attention-deficit hyperactive disorder (ADHD) and autism spectrum (23).

3.2 Mechanisms of action

VPA is known to acts via various ways. As described by Bourin M (2020), there are several pathways identified to be affected following administration of VPA (24). It is well known that VPA will acts on the central nervous system by potentiating the activity of gamma-aminobutyric acid (GABA) (16). It also acts by inhibiting ion channel that leads to repolarization of the membrane that subsequently stabilizing the membrane (25). VPA also was found to act as a glutamate antagonist, reducing the activity of glutamate/N-methyl-D-aspartate receptors in the central nervous system (1). It action on the signaling pathway of

inositol has been hypothesized to reduce the inositol de novo synthesis (26) that is associated to bipolar disorder.

VPA was also found to be responsible ot activation of various signalling pathyways including extracellular signal-regulated kinase pathway (ERK) (27) that is associated with neurogenesis, dendritic arborization, and neuronal plasticity, and activation of mitogen activated protein kinases (MAPK) (28) for the neuroprotective effect of VPA.

Aside from activation pathways, VPA was also found to decrease or inhibit pathways. This include inhibition of arachidonic acid phospholipid A2 (PLA2) pathway that is known to be responsible to affect membrane excitability, gene transcription, sleep pattern, and memory among others (29). VPA also found to inhinbit glycogen synthase kinase (GSK3) that is responsible to cell cycle progression and the structure of neuron cell survival (30).

3.3 VPA in the brain

Ischaemic stroke is one of the most common subtypes of stroke and current treatment options are limited to thrombolytic therapy within an extremely narrow time frame (31).

Histone deacetylase (HDAC) is an enzyme associated with brain disorders, including ischaemic stroke, autism, Alzheimer's disease and depressive disorders. VPA is known to be a non-specific HDAC inhibitor and is independent of the inhibition of histone deacetylase 9 (HDAC9), an enzyme involved in the pathogenesis of ischaemic stroke (32).

It was found that co-administration of VPA and resveratrol showed a synergistic neuroprotective effect in the treatment of post-ischaemic brain damage, which was dose-dependent (34). In the in vitro oxygen glucose deprivation (OGD) study, VPA showed neuroprotective properties by inhibiting class I HDACs at a low dose in combination with resveratrol or at a higher dose when used alone (34). A study by the group found that VPA exerts similar neuroprotective effects via inhibition of HDAC3 expression and activity (35).

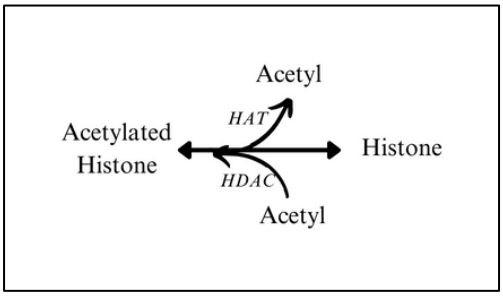

Figure 1 Roles of histone deacetylase (HDAC) and histone acetyl transferase (HAT) in histone acetylation and deactylation.

HDAC has been widely studied with 11 subtypes identified and grouped into 4 classess that responsible to various bodily functions (35). These results will benefit trauma patients who need immediate treatment for bleeding or brain injury. On the other hand, the action of VPA as an HDAC and glycogen synthase kinase-3β (GSK-3) inhibitor suggests that it is beneficial in patients with spinal cord injury, as it has neuroprotective and neurogenetic effects (36).

Similar observations were made in animal studies on the role of VPA in the prevention of chronic constriction injury-induced neuroinflammation and neuronal death (34). The study concluded that administration of VPA reduced the concentration of proinflammatory cytokines in the sciatic nerve, spinal cord and spinal ganglia of rats in the chronic constriction injury model, and VPA treatment reduced the expression of Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (pNFκB)/ Inducible Nitric Oxide (iNOS) / Cycloxygenase-2 (COX -2) and reduced the expression of pAkt / pGSK-3β in the salience network, dorsal root ganglion and spinal cord of rats after chronic constriction injury (37).

Although promising, further studies to better understand its role in humans would be urgently needed.

3.4 VPA and respiratory system

Based on their 10-year study of 16228 patients with subarachnoid haemorrhage (SAH), Liao et al. reported that VPA users had a significantly lower incidence of pneumonia and 16% reduced risk of acute respiratory failure, independent of neurological and cardiovascular dysfunction (38). The group postulated that this observation was due to the role of VPA as an HDAC inhibitor, which has a potent anti-inflammatory effect. At SAH, it is associated with increased release of proinflammatory cytokines, formation of reactive oxygen species and production of neutrophil elastase, which progressively promote vascular permeability towards acute lung injury and also acute lung failure (38).

The lung-protective effect of VPA was further supported by Bhagarva et al, as it was shown to inhibit the production of nuclear factor-κβ (NF-κB), tumour necrosis factor-α (TNF-α) and interleukin-6 (IL -6) and other chemokines that attract neutrophils that subsequently cause damage to the lung (39).

As VPA has been shown to be beneficial in acute respiratory distress syndrome (ARDS), it is thought that the same effect could be achieved in COVID -19 patients, as these patients have excessive release of proinflammatory cytokines in the respiratory system (40). Studies later observed that VPA have positive roles in COVID-19 infection (41, 42, 43).

3.5 VPA and liver

The effect of VPA on the liver is well known. Data from the World Health Organisation (WHO) show that VPA was the third leading cause of drug-related deaths in the liver based on surveillance data between 1968 and 2003 (44). This was due to the excretion of VPA via the liver with a life-threatening side effect including hepatotoxicity occurring during the first 6 months of treatment. The hepatotoxicity can varies from minimal or asymptomatic to life-threatening/death condition, not just minor increases in the liver enzyme (45).
It has also been suggested that VPA may cause liver toxicity via the formation of reactive VPA metabolites, inhibition of fatty acid-β oxidation, increased oxidative stress and genetic polymorphisms of certain enzyme genes such as carbomyl phosphate synthetase 1 (CPS1), polymerase gamma (POLG), glutathione S-transferases (GSTs), superoxide dismutase 2 (SOD2), uridine 5'-diphospho-glucoronosyltransferase (UGTs) and cytochromes P450 (CYPs) (46, 47). It has been highlighted that disturbance to VPA regulation might leads to the formation of toxic metabolites (48) that leads to neurological and mental disorders (49), fetal malformations (50), neuroendocrine dysfunction (51), and impaired hematopeiotic homeostasis (52), among others.

Chen et al. (2015) found in their study that patients with carnitine deficiency are at higher risk of VPA-induced liver injury (53) and therefore recommended that carnitine supplementation may be beneficial in VPA-induced liver injury to protect the liver from toxins.

In children, VPA-induced drug-induced liver injury (DILI) occurs more frequently than in adults, with an estimated 1 in 600 incidence of hepatotoxicity in children aged two years and younger (54). The USFDA database indicates that VPA causes the most DILI problems in children (55).
Therefore, paediatricians need to be aware of this potential liver toxicity in children and, should it occur, early action is urgently needed to ensure patient safety.

3.6 VPA and the cardiovascular system

Antiepileptic drugs are known to affect the cardiovascular system. It has been suggested that VPA use is associated with

sudden unexpected death in epilepsy, due to an increased risk of prolonged QT (56). Aghabiklooei (2015) showed in her study of 196 VPA intoxicated patients that 19.9% had prolonged QT intervals (56).

Similar results were observed for prolonged QT intervals in seizure patients receiving VPA compared to healthy non-epileptic patients (57). The study was conducted in 129 subjects and perhaps larger studies are needed to understand the effects of taking VPA on the heart.

VPA ingestion is also associated with hypertension in 1-5% of patients through several mechanisms, including increasing gamma-aminobutyric acid (GABA) neurotransmitters, blocking sodium channels and inhibiting neuronal excitation mediated by glutamate/N-methyl-D-aspartate (NMDA) receptors (58). Further background information such as non-drug risk factors including gender, age, metaboliser status, history of heart disease and drug history is required to establish an association with the occurrence of the heart-related abnormalities.

The HDAC inhibitor properties of VPA may have a protective effect on the heart, so its use may be beneficial in the treatment of supraventricular arrhythmias, myocardial infarction, cardiac remodelling, hypertension and fibrosis, as reported by Tian et al (59). A study in myocardial ischemic rats in which VPA was injected intraperitoneally resulted in a decrease in the release of lactate dehydrogenase (a marker of myocardial damage), as well as decreased Bax and increased Bcl2 expression (prevents cell apoptosis), which could have a positive effect on myocardial outcome at post infarction (59). The team found that forkhead box protein (Foxm1) expression was 4-fold higher in the presence of VPA than in the absence of VPA (59). The protein Foxm1 is responsible for cardiomyocyte proliferation (60).

The findings suggested that VPA may be beneficial in the treatment of acute myocardial infarction which could be important.

3.7 VPA and bone

Long-term treatment with VPA is known to be associated with vitamin D deficiency, osteoporosis, bone loss and an increased risk of fractures (61). These adverse effects were listed by the USFDA following the post-marketing surveillance report. Arora et al. (2016) pointed out that VPA is associated with decreased bone mass density and increases the risk of fractures, thus requiring close monitoring, prevention and treatment of bone disease in patients receiving VPA (62).

A meta-analysis by Xu et al. (2019) also concluded that prolonged treatment with VPA monotherapy of more than 2 years reduced vitamin D levels in children with epilepsy compared with healthy children (63). Therefore, vitamin D supplementation would help children with prolonged VPA treatment from bone malformations.

Significantly low vitamin D levels (less than 20 ng/ml) were found in 28 paediatric patients with epilepsy receiving monotherapy with VPA, despite normal growth, no limitation of physical activity and adequate sun exposure (64). Similar observations in vitamin D deficiency following VPA use in pediatric patients were reported by others (63, 65).

Pitetzis and co-workers noted in their review that VPA mediates changes in several bone activities in addition to reducing vitamin D levels. These include downregulation of osteoblast proliferation, changes in collagen synthesis and also indirect effects through endocrine systems such as hypogonadism, hypothyroidism, hypercortisolaemia and carnitine deficiency (66).

The effect of VPA on bone still needs to be better understood. New evidence, such as the association with osteoporosis mediated by a decrease in vitamin D levels, still needs to be better understood. In addition, current evidence indicates that

paediatricians need to be cautious and aware when administering VPA as monotherapy in children.

3.8 VPA side effects

3.8.1 Weight gain, non-alcoholic fatty liver disease, and insulin resistance

VPA -related weight gain and obesity have been frequently reported in association with other metabolic disorders such as insulin resistance, dyslipidaemia, metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD) (67). In children, long-term studies with VPA have demonstrated weight gain and insulin resistance (68).

Metabolic disturbances in patients treated with VPA were further confirmed by the observation of Chang et al. (2010) in their study. The two-arm study of 119 healthy volunteers and 77 bipolar patients indicated that VPA was the cause of the metabolic disturbances observed in bipolar patients treated with VPA (57).

So far, the weight gain induced by VPA is not age-dependent, as noted by Tian et al. (2019) (59). It has been suggested that VPA -induced weight gain is multifactorial and occurs through multiple pathways. Several neuropeptides and cytokines are mediated centrally and peripherally (Figure 3) and are thought to be involved in weight gain (56).

An increase in lipid levels after treatment with VPA has also been reported in association with weight gain. In a study of 60 subjects randomly assigned to receive either VPA or carbamazepine, the VPA treatment group was found to have a high body mass index, high triglyceride levels and low high-density lipoprotein levels (69). Despite the increase in lipid profile, the group concluded that VPA was safe and the occurrence of insulin resistance was not significant. (69).

In a separate study, Rehman et al (2017) pointed out that VPA-induced weight gain is associated with changes in insulin and leptin levels. It was found that VPA also significantly increased insulin levels and insulin resistance (HOMA-IR) by inhibiting several metabolic pathways such as glucose uptake, glycogenesis and glucose oxidation (70, 71). Later, it was concluded that VPA increases the risk of metabolic syndromes such as hyperinsulinaemia, insulin resistance and oxidative stress.

Perhaps the occurrence of metabolic disorders in patients receiving prolonged treatment with VPA should be closely monitored by both the physician and the pharmacist.

3.8.2 Alopecia and hair growth

According to the USFDA, VPA-induced alopecia was found to be the most common cosmetic adverse reaction. The report concurred with a review by Wang et. al (2019), who reported that VPA-induced alopecia occurred in 6 to 12% of patients based on their observation of 42 patients (72).

Anagen effluvium is the form of hair loss that occurs when hair is actively growing during the anagen phase of the hair cycle. This prevents the natural division of matrix cells that form new hair and causes the hair follicles to reach their (telogen) resting stage and fall out too early (73). Alopecia is thought to be caused by VPA and is related to its duration of use (74). It has been suggested to start with a low dose and gradually increase the dose to reduce VPA -induced hair loss (74).

Another mechanism proposed for VPA-mediated hair loss is the suppression of biotinidase activity which is responsible for the recycling of biotin. A study in 75 paediatric patients found that VPA dose and biotinidase activity were inversely proportional (74). Taking biotin, zinc and selenium supplements may help reduce further hair loss.

In contrast to oral intake of VPA, which causes hair loss, tests with topical application of VPA have shown hair

regeneration. VPA has been reported to inhibit glycogen synthase kinase 3β (GSK-3β) and activation of the Wnt/β-catenin pathway, which in turn correlates with hair regeneration and anagen activation (75). A study of male patients with moderate androgenic alopecia treated with VPA spray for 24 weeks reported a significant increase in hair number compared to placebo (76).

Further evidence on the effect of VPA on hair loss and regeneration is urgently needed. Different modes of application - internal and topical - resulted in contrasting hair outcomes.

3.8.3 Nocturnal enuresis

Nocturnal enuresis has been identified as a post-marketing side effect in VPA users and has been listed by the USFDA. Nocturnal enuresis is usually underdiagnosed or neglected by physicians. A study showed that secondary nocturnal enuresis is common in children taking VPA, with prevalence ranging from 15% to 25% at 5 years of age and decreasing with age (77). The pathophysiology of VPA - induced nocturnal enuresis is still unconfirmed. It is thought to be a multifactorial enuresis mediated by various causative factors such as maturation delays of the central nervous system, sleep disturbances, an undercapacitated bladder, urinary tract malformations, inadequate nocturnal antidiuretic hormone secretion and psychogenic factors (78). It could also be related to an increase in deep sleep after taking VPA (78), who could not control their urination to wake them up at night.

3.8.4 Teratogenicity

Because of the known teratogenic effects of VPA, pharmacists are encouraged to advise women of childbearing age of the risks and problems each time they have dispensed VPA and to give them a warning card. It has been reported that VPA use may increase the risk of congenital malformations in newborns to 6-12% compared to 2-3% in the general population (79).

Based on their analysis of data from the European Registry of Antiepileptic Drugs and Pregnancy (EURAP) with over 3900 pregnant mothers taking antiepileptic drugs, Tomson et al. (2011) reported that the occurrence of malformations is dose-dependent and that patients on VPA have a higher risk of malformations compared to other antiepileptic drugs (80).

Commonly reported foetal malformations associated with VPA include spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly and craniosynostosis of the offspring.

In a prospective, multicentre cohort study of women taking antiepileptic drugs by Meador and co-workers, significantly lower IQ was observed in the infants of mothers taking VPA compared with other antiepileptic drugs (81). The group also suggested that VPA should be avoided in women of childbearing age.

Due to unfavourable side effects, the UK health authorities have proposed a 'pregnancy prevention programme' for the prescription involving VPA (82):

- The possibility of pregnancy in the woman and pregnancy tests must be determined before and during therapy.
- The woman must be counselled about the risk to her unborn child from VPA and the importance of using contraception while taking the drug.
- Women taking VPA are encouraged to have an annual specialist review, such as a risk assessment 4) There must be a visual warning on the pack of VPA about the dangers of VPA in pregnancy.

Therefore, healthcare providers can encourage discussion of the benefits and risks of taking VPA in women of

childbearing age each time VPA is dispensed.

4.0 Pharmacogenomic of VPA

VPA pharmacogenomic profile indicates that genetic variations can significantly impact its efficacy and potential side effects.

4.1 Cytochrome (CYP) Variants

Approximately 15-20% of VPA is known to be metabolised via specific human cytochrome P450 (CYP) enzymes such as CYP2C9, CYP2B6 and CYP2A6 to 4-ene valproate and hydroxy metabolites, which have been associated with VPA -induced liver injury (83, 84).

In paediatric patients, Budi et al. suggested that CYP2C9-catalysed oxidation is the major metabolic pathway for VPA (85). They also found that CYP2C9 status-guided VPA treatment in children led to a reduction in VPA misdosing and avoidance of side effects (86). In children carrying at least one or two CYP2C9 wild-type alleles (CYP2C9* 1/*1, CYP2C9* 1/*2 or CYP2C9* 1/*3), controlled VPA treatment may result in a better response (86).

The usual recommended dose may be given to children with normal CYP2C9 expression (CYP2C9*1/*1); the dose may be reduced in children with heterozygous genotype (CYP2C9*1/*2 or CYP2C9*1/*3) and low CYP2C9 expression and increased in children with high CYP2C9 expression (CYP2C9*1/*1). In cases of dual loss-of-function CYP2C9 alleles (CYP2C9*2/*2, CYP2C9*3/*3 or CYP2C9*2/*3) in children, it is recommended that an alternative antiepileptic drug (other than VPA) be administered due to the poor metabolism of VPA (63, 86, 87).

4.2 Uridine diphosphate Glucuronosyl Transferase (UGT) Variants

It is also known that glucuronidation (including UGT1A1, UGT1A9, UGT1A4, UGT1A6, UGT1A3, UGT2B7 and UGT2B15) is the major route of VPA excretion, with approximately 20-70% excreted as glucuronide conjugates in the urine (84). The three commonly reported non-synonymous polymorphisms of UGT1A6, including S7A, T181A and R184S, had no significant effect on VPA dose requirements and concentrations in children (88). Contrasting results were observed in studies of adult subjects. A study of 162 adult epilepsy patients on VPA monotherapy and stable epilepsy treatment showed that patients with the UGT1A6 allele 19 T > G, 541A > G and 552A > C appeared to require a higher VPA dose and lower concentration-to-dose ratio (CDR) than non-carriers (89). Another observational study of 114 patients with epilepsy also showed no correlation between UGT2B7 and VPA efficacy (90). Undoubtedly, genetic variations influence the effect of VPA on the body. It is important to consider genetic differences when initiating and maintaining VPA treatment.

4.3 Toxicities and Adverse Effects Genetic Variants

VPA ingestion has been associated with serious adverse drug reactions, including liver damage, toxicity to mitochondria, teratogenicity, encephalopathy with hyperammonaemia and other adverse effects (84).

Several adverse events associated to gene polymorphisms have been found to be induced by VPA. These include the T1405 polymorphism of the CPS1 gene, which increases the incidence of hyperammonaemia in Caucasian patients (8), the Val16Ala polymorphism of the SOD2 gene, which leads to high serum levels of γ-glutamyltransferase in Japanese patients (91), and the LEPR and ANKK1 gene polymorphisms associated with weight gain in Han Chinese (92) are some of the examples of VPA toxicities observed in a specific population.

A better understanding of the gene polymorphism and the use of VPA is therefore urgently needed in each population group to ensure its safe use.

5.0 Conclusion

This review highlighted much new information on VPA in all aspects of its pharmacokinetics, pharmacodynamics and pharmacogenomics. In terms of pharmacokinetics, the new information includes interaction with new drugs and serum concentration associated with variables. On the other hand, VPA has an effect on various systems and organs. Recent evidence suggests that it has neuroprotective and neurogenetic effects in brain infarcts and protects the lungs by reducing the risk of patients with acute respiratory failure. VPA has also been found to have a higher risk of hepatotoxicity in children and to have a significant effect on metabolic disorders after prolonged use. Gene polymorphisms of CYP450, UGT, CPS1, SOD2, LEPR, ANKK1 and SCN1A are known to have adverse effects in some populations.

Conflicts of interest

The authors declare no conflict of interest.

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